

ORIGINAL ARTICLE

Real-world use of cardioprotective glucose-lowering drugs in patients with type 2 diabetes and cardiovascular disease: A Danish nationwide cohort study, 2012 to 2019

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Abstract

Aims: To investigate temporal trends in time to initiation of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide 1 analogues (cardioprotective glucose-lowering drugs [GLDs]) in patients with a new dual diagnosis of type 2 diabetes (T2DM) and cardiovascular disease (CVD).

Materials and methods: In a cohort study, we identified patients with a new dual diagnosis of T2DM and CVD using linked healthcare data from nationwide registries on drug prescriptions and diagnosis codes. For each calendar year between 2012 and 2018, we examined time to initiation and cumulative user proportions (CUPs) for cardioprotective GLD use 1 and 2 years after the dual diagnosis.

Results: Among all individuals living in Denmark in the period 2012 to 2018, 41 733 patients with a new dual diagnosis of T2DM and CVD were identified (median [interquartile range] age 71 [64–79] years, 61% male, and 57% with CVD as the latest diagnosis). Incidence curve slopes and 1- and 2-year CUPs for cardioprotective GLDs increased during the study period (1-year CUP 4.0%, 95% confidence interval [CI] 3.6–4.5) in 2012 to 14.7, 95% CI 13.7–15.7, in 2018; 2-year CUP 5.5, 95% CI 5.0–6.1, in 2012 to 16.7, 95% CI 15.8–17.7, in 2018). T2DM patients with CVD as the second (latest) diagnosis had higher 1-year CUPs than CVD patients with T2DM as the latest diagnosis: 2012: 7.0 (95% CI 6.2–8.0) versus 1.4 (95% CI 1.0–1.8); 2018: 18.1 (95% CI 16.8–19.6) versus 10.0 (95% CI 8.8–11.3).

Conclusions: In patients with T2DM and CVD, the incidence of cardioprotective GLD initiation increased between 2012 and 2018, however, within 2 years of dual diagnosis, it remained low.

KEYWORDS

antidiabetic agents, cardiovascular disease, pharmacoepidemiology, type 2 diabetes

1 | INTRODUCTION

Cardiovascular risk remains an important cause of premature mortality in patients with type 2 diabetes (T2DM), with an approximately two-fold higher risk of cardiovascular death compared to people without diabetes.¹ The pathophysiology of T2DM and cardiovascular disease (CVD) is intimately linked and, when a diagnosis of CVD is established, patients with T2DM have more advanced CVD than those without diabetes.² Accordingly, patients with T2DM and CVD have a worse prognosis for recurrent CVD events than non-diabetic individuals with CVD.^{3,4} It is therefore of paramount importance to initiate and intensify secondary prophylaxis in these patients with a dual diagnosis of T2DM and CVD to reduce the risk of recurrent cardiovascular events and cardiovascular death.

Until 2015, the effectiveness of non-insulin glucose-lowering drugs (GLDs) was controversial in secondary CVD prevention,^{5,6} however, two groups of GLDs have since been shown to reduce the risk of recurrent cardiovascular events. Sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) analogues have been studied in large cardiovascular outcome trials with the aim of demonstrating cardiovascular safety, but surprisingly, the study drugs substantially reduced the risk of cardiovascular events, including hospitalization for heart failure, in patients with established CVD.^{7–13} In patients without established CVD but multiple CVD risk factors, SGLT2 inhibitor use was associated with a lower risk of hospitalization for heart failure¹⁴ and GLP-1 analogue use was associated with a lower risk of major adverse events.¹⁵ Real-world data have confirmed the results of the cardiovascular outcome trials.^{16,17} In the present paper, these two drug classes are therefore referred to as cardioprotective GLDs. The first of these trials were published in late 2015 and early 2016, and have led the European Association for the Study of Diabetes (EASD) and the American Diabetes Association to a recommendation of GLP-1 analogues and SGLT2 inhibitors as add-on to metformin in T2DM with established CVD.¹⁸ In Denmark, a similar recommendation was put forward by the National Health Institute in October 2017, and implemented in national guidelines by the scientific societies in May 2018. In September 2019, the European Society of Cardiology, in collaboration with the EASD, further emphasized the importance of cardioprotective GLDs in their joint guidelines on diabetes and CVD by recommending the use of these drugs regardless of glycated haemoglobin (HbA1c) levels or prior use of metformin.¹⁹

“Real-life” use of new cardioprotective GLDs in patients with T2DM and established CVD in routine clinical care has been sparsely investigated.^{20–24} Whether results of the recent large cardiovascular outcome trials have had an impact on the use of cardioprotective GLDs is unknown. We therefore aimed to describe the use of cardioprotective GLDs in patients with T2DM and CVD during the period 2012 to 2018. Specifically, we aimed to examine the time to initiation and cumulative user proportions (CUPs) of GLDs in patients with T2DM who received a first diagnosis of CVD, and in patients with established CVD and new T2DM. In addition, we aimed to investigate whether the time to initiation of cardioprotective drugs differed according to the latest diagnosis (T2DM or CVD).

2 | METHODS

2.1 | Design, setting and patients

This was a population-based cohort study. The source population consisted of all individuals who lived in Denmark in 2012 to 2018. The study population included patients with a first dual diagnosis of T2DM and CVD. T2DM patients were defined as individuals with ever-use of any GLD (metformin, sulphonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors or combination products) or insulin (according to the Anatomical Therapeutic Chemical [ATC] classification system).²⁵ Patients under the age of 30 years on the date of first insulin prescription, and patients under the age of 15 years on the date of any GLD prescription were excluded as likely type 1 diabetes patients.^{21,26,27} The date of first community-based prescription for any GLD was considered the T2DM diagnosis date.

Patients with CVD were defined as individuals with first occurrence of one or more International Classification of Diseases (ICD)-8/-10 codes for ischaemic heart disease, cerebrovascular disease, peripheral artery disease, or heart failure or associated procedural codes^{28,29} (Table S1). The CVD diagnosis date was defined as the discharge date from an inpatient admission with a primary or secondary code of CVD, or the first contact date in a hospital clinic outpatient course with a primary or secondary code of CVD. The date on which patients received their second (latest) diagnosis (T2DM or CVD) according to the above definitions was defined as the index date of a dual diagnosis of T2DM and CVD.

2.2 | Data sources

The study was based on the population-based registries described below.

The Civil Registration System: This holds records of central personal registry number, address, marital status, emigration and immigration status and date of death (if any) of the entire population of Denmark since 1968. This system can be used to link all Danish registries containing central personal registry numbers.³⁰

The Danish National Patient Register: This includes information of all hospitalized patients since 1977 and on outpatient hospital contacts since 1995. The register contains information about the date of admission, discharge, diagnosis codes and surgical procedures. From 1977 to 1993, diagnosis codes were coded with reference to the ICD-8 classification and, from 1994 onwards, they have been coded according to ICD-1014.

The National Database of Reimbursed Prescriptions: This contains complete information on all prescriptions dispensed at community pharmacies in the Danish regions since 2004. Record information about the drug user including civil registration number, age, gender, residence, ATC code of the drug, package size, and date of dispensing. Prescription data were available until and including May 2019.

The Clinical Laboratory Information System Database: This contains detailed population-based laboratory data from both primary and secondary care for Northern Denmark (ie, the North and Central Denmark regions, population in 2013 approximately 1.8 million, or 30% of Denmark's population) with high completeness since the early 2000s.³¹ Data on HbA1c, LDL cholesterol and estimated glomerular filtration rate (eGFR) can be extracted from this registry up to 2018.

2.3 | Variables

Diagnosis and procedural codes for CVD and other diseases are shown in Table S1. ATC codes for all drugs including GLDs are shown in Table S2. For all patients, we obtained data on age, gender, comedications (cardiovascular medications including anti-hypertensives, antiplatelet therapy, lipid-lowering drugs, proton pump inhibitors, diuretics), and diabetes duration (years since first recorded diabetes therapy). For the regional subcohort, we additionally obtained HbA1c (last measured value within 12 months), eGFR based on last measured creatinine, and LDL cholesterol values from the Clinical Laboratory Information System Database.

The study outcome was prescription of a cardioprotective GLD, defined as initiation of any type of SGLT2 inhibitor or GLP-1 analogue. GLP-1 analogues were first introduced in Denmark in 2007 (exenatide), whereas the first SGLT2 inhibitor was introduced in 2012 (dapagliflozin). An overview of the GLP-1 analogues and SGLT2 inhibitors, their introduction to the Danish market, and the publication dates of the respective cardiovascular outcome trials is given in Table S3.

2.4 | Statistical analyses

We characterized patients at the onset of their latest diagnosis (T2DM or CVD), that is, on the index date of the dual diagnosis. This included a characterization of baseline GLD use on the index date, based on prescriptions filled within 100 days before the index date (among primary T2DM patients who received the second diagnosis of CVD on the index date) and prescriptions filled on the index date itself. Patients who had not redeemed any cardioprotective GLD at any time (up to 1 year prior to the index date) were considered naïve for cardioprotective GLDs. For biochemical variables, we identified the last measured value before or on the date of their latest diagnosis.

For each calendar year between 2012 and 2018, we identified patients with a first-time dual diagnosis of T2DM and CVD. For these patient cohorts, namely, in those with latest diagnosis in 2012, in 2013, in 2014 and so on, we constructed cumulative incidence curves for cardioprotective GLD use. Curves were adjusted for competing risk of death. From the curves, we assessed the 1-, and 2-year CUP of patients receiving a cardioprotective GLD. Patients who were new or prevalent users of cardioprotective GLDs already on the index date of their dual diagnosis were included in the CUPs at 1 or 2 years,

because our primary aim was to assess the overall likelihood of patients with T2DM and CVD receiving a cardioprotective GLD in clinical practice.

Continuous variables are presented with mean (\pm SD) and median (25th and 75th percentiles) as appropriate. Dichotomous data are presented as n (%).

3 | RESULTS

3.1 | Patient characteristics

We identified 41 733 patients with a first dual diagnosis of T2DM and CVD in Denmark between 2012 and 2018 (18 119 patients [47%] with T2DM as the latest diagnosis and 23 966 patients [53%] with CVD as the latest diagnosis [Table 1]). Patients had a median age of 71.4 years, 61% were male and only 8% of patients had no comorbidities. In the combined study population, 88% of patients received one or more drugs protecting against CVD: antiplatelet agents, anti-hypertensive agents or lipid-lowering agents, however, drug use within each of these drug classes was markedly lower (range 51%–82%). Biguanides were the most frequently used GLD, and the use of cardioprotective GLDs was generally low at the time of the latest dual diagnosis. In the subcohort of patients from Northern Denmark, the median HbA1c level was 53 mmol/mol (7.0%), the median LDL cholesterol level was 2.0 mmol/L and the median eGFR was 74 mL/min per 1.73 m².

3.2 | Time to initiation of a cardioprotective GLD

Figure 1 shows incidence curves of cardioprotective GLDs in patients with a dual diagnosis of T2DM and CVD. From 2012 to 2018, the slope of the curves increased, corresponding to a gradually faster initiation of cardioprotective GLDs, both in the entire study population (Figure 1A) and in the two separate groups (Figure 1B,C). For the entire population, incidence curves in 2012 to 2015 had a somewhat gradual, linear increase over several years of the study period. In the period 2016 to 2018, incidence curves rose much more steeply within the first 6 months of the dual diagnosis, after which the steepness of the curves decreased and continued to increase approximately linearly for the rest of the follow-up period. This pattern was also observed in the two separate groups, with the exception of patients with established CVD and new T2DM in 2012, for whom the slope increased non-linearly over the entire follow-up period.

In patients with established CVD and a new T2DM diagnosis in 2012, 10% of patients had received a cardioprotective GLD after 6.1 years of follow-up. In 2018, the same proportion (10%) of patients with a new T2DM diagnosis received a cardioprotective GLD already after 1.0 year of follow-up (Figure 1).

In patients with established T2DM and a new CVD diagnosis in 2012, 15% had received a cardioprotective GLD after 4.6 years of

TABLE 1 Characteristics of patients with type 2 diabetes and cardiovascular disease dual diagnosis

	All patients with dual diagnosis of T2DM and CVD (N = 41, 732, 100%)	CVD with new T2DM (N = 18, 118, 43%)	T2DM with new CVD (N = 23 614, 57%)
Men, n (%)	25 420 (61)	11 454 (63)	13 966 (59)
Women, n (%)	16 312 (39)	6664 (37)	9648 (41)
Median (IQR) diabetes duration, years	1.70 (0.00, 9.60)	0.00 (0.00, 0.00)	8.40 (4.00, 14.40)
Median (IQR) age, years	71.40 (63.50, 79.10)	70.80 (62.50, 78.20)	72.00 (64.10, 79.70)
Age <50 years, n (%)	1692 (4)	883 (5)	809 (3)
Age ≥50 and <60 years, n (%)	5549 (13)	2605 (14)	2944 (12)
Age ≥60 and <70 years, n (%)	11 319 (27)	5028 (28)	6291 (27)
Age ≥70 and <80 years, n (%)	13 834 (33)	5988 (33)	7846 (33)
Age ≥80 years, n (%)	9338 (22)	3614 (20)	5724 (24)
Ischaemic heart disease, n (%)	9426 (23)	6062 (33)	3364 (14)
Heart failure, n (%)	9641 (23)	6829 (38)	2812 (12)
Cerebrovascular disease, n (%)	11 297 (27)	8663 (48)	2634 (11)
Peripheral artery disease, n (%)	6054 (15)	4612 (25)	1442 (6)
Any antiplatelet treatment, n (%)	22 699 (54)	11 888 (66)	10 811 (46)
Aspirin, n (%)	18 240 (44)	8777 (48)	9463 (40)
ADP receptor blockers, n (%)	7044 (17)	4772 (26)	2272 (10)
Statins, n (%)	27 550 (66)	13 003 (72)	14 547 (62)
Any anti-hypertensive treatment, n (%)	36 828 (88)	16 317 (90)	20 511 (87)
ACE inhibitors, n (%)	16 920 (41)	7460 (41)	9460 (40)
ARBs, n (%)	12 094 (29)	4713 (26)	7381 (31)
Calcium-blockers	15 069 (36)	6028 (33)	9041 (38)
Beta-blockers, n (%)	23 364 (56)	8526 (47)	14 838 (63)
Thiazides, n (%)	7871 (19)	3527 (19)	4344 (18)
Loop diuretics, n (%)	22 354 (54)	10 584 (58)	11 770 (50)
Proton pump inhibitors, n (%)	14 474 (35)	6632 (37)	7842 (33)
Oral steroid, n (%)	5565 (13)	2872 (16)	2693 (11)
SGLT2 inhibitors, n (%)	516 (1)	56 (0)	460 (2)
GLP-1, n (%)	1635 (4)	145 (1)	1490 (6)
DPP-4 inhibitors, n (%)	3101 (7)	610 (3)	2491 (11)
Biguanides, n (%)	29 359 (70)	15 927 (88)	13 432 (57)
Sulphonylureas, n (%)	3289 (8)	387 (2)	2902 (12)
Glitazone, n (%)	13 (0)	0 (0)	13 (0)
Insulin, n (%)	7975 (19)	1550 (9)	6425 (27)
Median (IQR) HbA1c, mmol/mol ^a	53 (48-63) (7.0% [6.5%, 7.9%])	53 (49-63) (7.0% [6.6%, 7.9%])	52 (45-62) (6.9% [6.3%, 7.8%])
Median (IQR) LDL cholesterol, mmol/L ^a	2.20 (1.60, 2.80)	2.20 (1.70, 2.90)	2.10 (1.50, 2.80)
Median (IQR) estimated GFR ^a mL/min per 1.73m ²	74.01 (54.99, 89.65)	75.66 (57.81, 90.06)	72.32 (52.07, 89.27)
eGFR < 60 mL/min per 1.73m ² , n (%) ^a	3838 (31)	1624 (28)	2214 (34)
eGFR < 30 mL-min per 1.73m ² , n (%) ^a	429 (3)	114 (2)	315 (5)

Abbreviations: ACE, angiotensin-converting enzyme; ADP, adenosine diphosphate; ARB, angiotensin II receptor blocker; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; IQR, interquartile range; SGLT2, sodium-glucose co-transporter-2; T2DM, type 2 diabetes.

^aRegional subcohort of patients with dual diagnosis of T2DM and CVD (total: N = 12 811, 100%; new T2DM: n = 5929, 46%; new CVD: n = 6882, 54%).

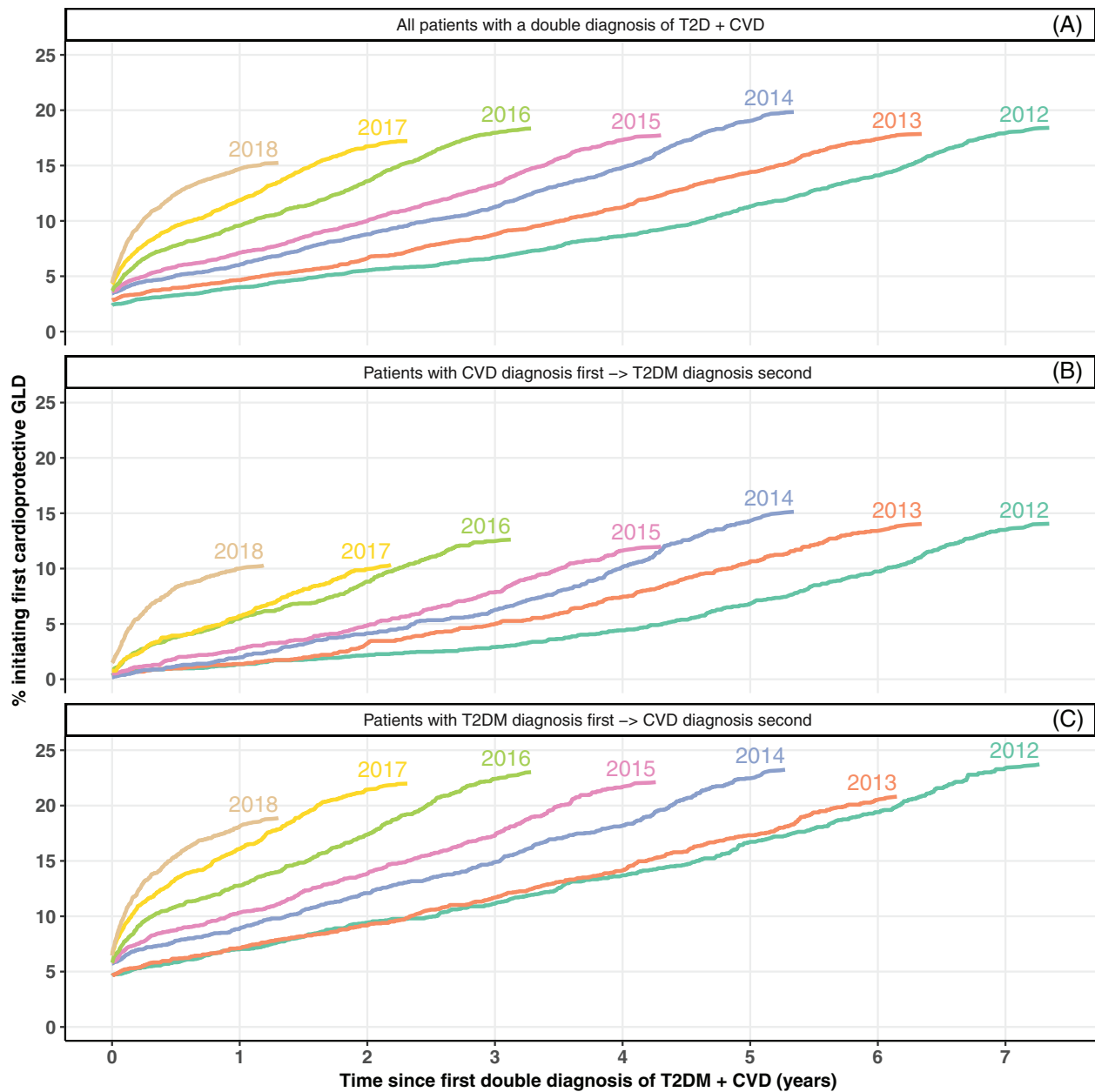


FIGURE 1 Time to initiation of cardioprotective glucose-lowering drugs (GLDs) in patients with a first dual diagnosis of type 2 diabetes (T2DM) and cardiovascular disease (CVD). **A**, All patients with a new-onset dual diagnosis of type 2 diabetes and cardiovascular disease. Prevalent users of cardioprotective GLDs are included in graph at time = 0. **B**, Patients with established CVD and new T2DM. **C**, Patients with established T2DM with new CVD. Prevalent users of cardioprotective GLDs are included in graph at time = 0. GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose co-transporter-2

follow-up. In 2018, the same proportion (15%) was reached after 0.5 years of follow-up in 2018 (Figure 1C). In 2012, only a very small proportion of patients with established T2DM and new CVD were already treated with a cardioprotective GLD before the date of CVD diagnosis (83/6661, 1.2%). This proportion increased each calendar year to 109/5394 (2.0%) in 2018.

In general, curve slopes for cardioprotective GLD use were less steep in patients with established CVD and new T2DM (Figure 1B), compared with patients with established T2DM and new CVD (Figure 1C). This difference was also observed when disregarding

patients who already received cardioprotective GLD on the index date, which was more frequently seen in the latter group with new CVD, as expected.

3.3 | One- and two-year CUPs of cardioprotective GLD

The 1- and 2-year CUPs of cardioprotective GLD users are presented in Table 2 and Figure 2. Both in the total study population and in the

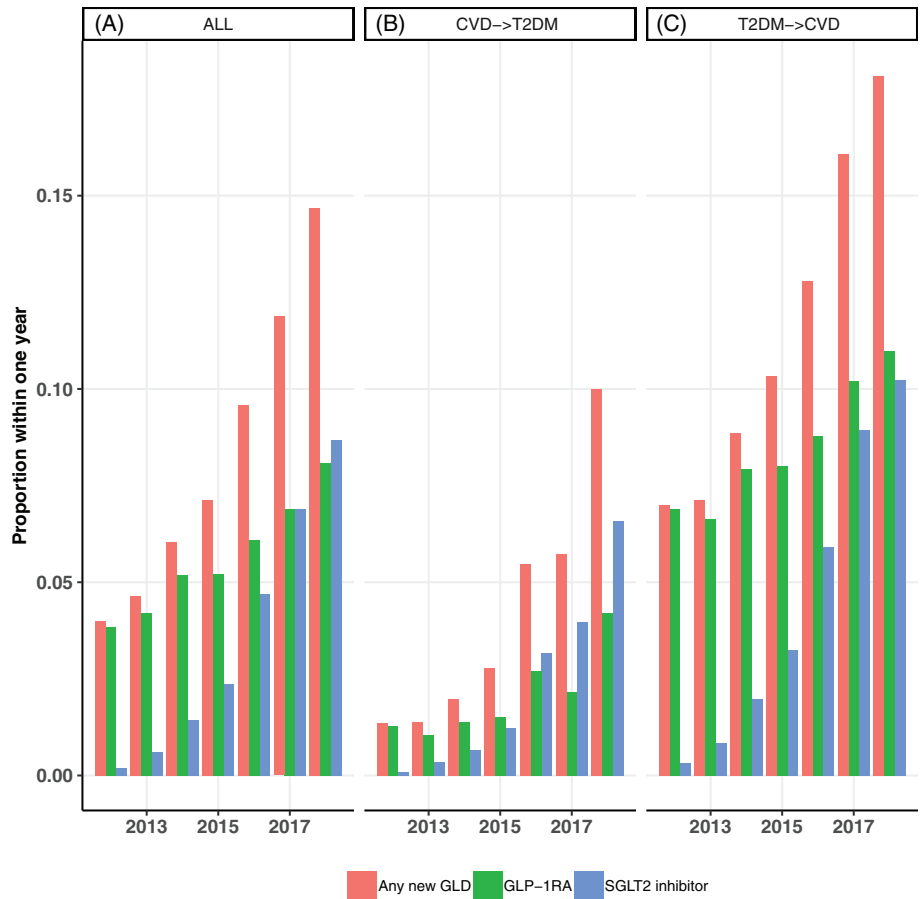
TABLE 2 One- and two-year cumulative incidence proportions of cardioprotective glucose-lowering drug initiation in patients with type 2 diabetes and cardiovascular disease

	Patients with established CVD and new T2DM							Patients with established T2DM and new CVD						
	2012	2013	2014	2015	2016	2017	2018	2012	2013	2014	2015	2016	2017	2018
1-year CUP														
Cardioprotective GLD ^a	1.4	1.4	2	2.8	5.5	5.7	10	7	7.1	8.9	10.3	12.8	16.1	18.1
GLP-1 analogue	1.3	1	1.4	1.5	2.7	2.2	4.2	6.9	6.6	7.9	8	8.8	10.2	11
SGLT2 inhibitor	0.1	0.3	0.7	1.2	3.2	4	6.6	0.3	0.8	2	3.2	5.9	8.9	10.2
2-year CUP														
Cardioprotective GLD ^a	2.2	3.2	4.2	4.8	8.8	9.9	10.3	9.4	9.2	12.1	13.8	17.4	21.4	18.9
GLP-1 analogue	1.9	2.3	2.7	2.6	4.1	4.3	4.4	9	8.1	9.8	9.8	11.3	13.8	11.9
SGLT2 inhibitor	0.3	1.1	1.7	2.7	5.8	6.9	6.8	1.1	2	4.3	5.9	9.5	12.1	10.7

Abbreviations: CIP, cumulative incidence proportion; CVD, cardiovascular disease; GLD, glucose-lowering drug; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2; T2DM, type 2 diabetes.

^aNew GLD defined as either a GLP-1 analogue or a SGLT2 inhibitor.

FIGURE 2 Proportions in treatment with new glucose-lowering drugs within 1 year after diagnosis of both type 2 diabetes (T2DM) and cardiovascular disease (CVD). **A**, All persons with dual diagnosis. **B**, Patients with established CVD and new T2DM. **C**, Patients with established T2DM and new CVD. GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT2, sodium-glucose co-transporter-2



two separate cohorts, the proportions of cardioprotective GLD users increased between 2012 and 2018. In the total population, 1- and 2-year CUPs were 4.0% (95% confidence interval [CI] 3.6–4.5) and 5.5% (95% CI 5.0–6.3) in 2012, versus 14.7% (95% CI 13.7–15.7) and 15.3% (95% CI 14.3–16.3) in 2018; in patients with established CVD

and new T2DM, 1.3% (95% CI 1.0–1.8) and 2.2 (95% CI 1.7–2.7) in 2012 versus 9.9% (95% CI 8.8–11.3) and 10.3% (95% CI 9.1–11.7) in 2018; in patients with established T2DM and new CVD, 7.0% (95% CI 6.5–8.0) and 9.4% (95% CI 8.4–10.6) in 2012 versus 18.1% (95% CI 16.8–19.6) and 18.9% (95% CI 17.5–20.4) in 2018.

Use of GLP-1 analogues and SGLT2 inhibitors both increased in this time period, however, the increase was most pronounced for SGLT2 inhibitor use (absolute increase in 1-year CUP between 2012 and 2018 in the total study population: GLP-1 use: 3.9% (95% CI 3.4–4.4) to 8.1% (95% CI 7.4–8.9); SGLT2 inhibitor use 0.2% (95% CI 0.1–0.3) to 8.7% (95% CI 7.9–9.5). In CVD patients with new T2DM (Figure 2B), SGLT2 inhibitors surpassed GLP-1 analogues over time as the most commonly prescribed cardioprotective GLD (7% of all cardioprotective GLD prescriptions initiated after 1 year in 2012, vs. 70% in 2018). In contrast, in T2DM patients with new CVD, the relative proportion of SGLT2 inhibitor use was level with GLP-1 analogues at the end of the study period in 2018 (4% of all cardioprotective GLD prescriptions after 1 year in 2012, vs. 56% in 2018).

The 1-year CUPs of cardioprotective GLDs per calendar year were generally lower in CVD patients with new T2DM compared with T2D patients with new CVD (Table 2). Similarly, the individual use of SGLT2 inhibitors and GLP-1 analogues 1 year after the dual diagnosis was lower in CVD patients with new T2DM compared with T2D patients with new CVD (Table 2).

4 | DISCUSSION

This nationwide study is the first to explore the time to initiation of cardioprotective GLDs in patients with a new-onset dual diagnosis of T2DM and CVD. These observational data show that the time to initiation of cardioprotective GLDs was significantly reduced between 2012 and 2018, and this was more pronounced for the initiation of SGLT2 inhibitors than GLP-1 analogues. Overall however, the 1- and 2-year cumulative proportions of cardioprotective GLD users remained low even in 2018. Finally, the initiation of cardioprotective GLDs was lower in CVD patients with T2DM as their latest diagnosis, compared with T2D patients with CVD as their last diagnosis.

Optimal medical treatment including antiplatelet drugs, anti-hypertensive drugs and cardioprotective GLDs is important for the prevention of recurrent CVD events in patients with T2DM and CVD,³² however, the proportion of patients with T2DM and CVD in optimal medical treatment remains low.³³ The low use of cardioprotective GLDs seems to be an important part of this undertreatment as documented in the present study and others.^{20,23,34} Arnold et al reported the real-world use of SGLT2 inhibitors and GLP analogues to be 5.2% and 6.0%, respectively, among a study population eligible for participation in the EMPAREG or LEADER trial³⁴ and similar proportions of cardioprotective GLD users were reported by others.^{20,23} Among initiators of cardioprotective GLDs in the period 2013 to 2018, three recent studies observed a relatively stable prevalence of patients with T2DM and CVD, although in the context of absolute increases in cardioprotective GLD use in the same time period.^{21,22,24}

The present study adds to these cross-sectional studies with data on the incidence of cardioprotective GLD treatment per calendar year for the period 2012 to 2018. Data were collected through linked healthcare registries covering all Danish citizens and, thus data were

not restricted to patients associated with a specific medical centre, study or insurance company. As expected, we observed a gradual increase in the incidence of cardioprotective GLD use per calendar year, most likely because of the coinciding publications of major cardiovascular outcome trials^{7–13} and international guidelines.^{18,19} This trend may continue in coming years as current and future scientific evidence will be better implemented in clinical guidelines, however, up until 2018, it is important to recognize that the vast majority of patients with T2DM and CVD were not treated with cardioprotective GLDs within 2 years after their dual diagnosis.

The low 1- and 2-year CUPs of cardioprotective GLD users may partly be explained by our patient selection that included patients with T2DM and any CVD, thus including more patients than would have been eligible for participation in the cardiovascular outcome trials. However, we included patients who are recommended to receive either an SGLT2 inhibitor or a GLP-1 analogue according to American and European guidelines^{18,19} except in the presence of drug contraindications. As an example, due to drug contraindications, patients with chronic kidney disease (eGFR < 60 mL/min per 1.73m²) were not recommended to initiate use of SGLT2 inhibitors according to contemporary guidelines up until 2019 when the CREDENCE trial was published (the CREDENCE trial showed lower risk of renal failure and cardiovascular events in patients with eGFR between 30 and <90 mL/min).³⁵ In the present study, the patients with eGFR <60 mL/min comprised 31% of our subcohort from Northern Denmark. Furthermore, we included patients at all ages and with comorbidities, and thus, in some patients the question of CVD protection from a cardioprotective GLD may not have been the most important intervention parameter, for example, due to short residual life expectations. Finally, the optimal timing of cardioprotective GLD initiation after an incident dual diagnosis of T2DM and CVD has never been tested in a randomized controlled trial. According to international guidelines, intensification with GLDs or insulin should be instituted if glycaemic control is not reached within 3 months,¹⁸ however, there are no recommendations regarding timing of cardioprotective GLD initiation. After 2018, international guidelines have suggested initiation of cardioprotective GLDs regardless of HbA1c level in the case of concomitant CVD.^{18,19} Patients in the major cardiovascular outcome trials of SGLT2 inhibitors and GLP-1 analogues had a minimum of 14 days (LEADER) interval between their CVD diagnosis and the inclusion in the respective study (minimum time between CVD event and randomization: range 14 days to minimum 3 months^{7–13}). Interestingly, in the cardiovascular outcome study of lixinate (ELIXA 2015), patients were included within 180 days of a coronary event (actual days between acute coronary event and randomization 72 days),³⁶ and whether these inclusion criteria had any effect on the neutral outcome of the study remains unknown (primary cardiovascular endpoint, lixinate vs. placebo: hazard ratio 1.02 [95% CI 0.89–1.17], non-inferiority [$P < 0.001$] and superiority [$P = 0.81$] of lixisenatide to placebo). Prognostic implications of the time from dual diagnosis of CVD and T2DM and initiation of cardioprotective GLDs should be explored in future studies.

In spite of the non-restrictive patient selection, we had expected higher proportions of patients being treated with a cardioprotective

GLD at 1 and 2 years after their dual diagnosis. We speculate that initiation of cardioprotective GLD use in this patient group may be challenged at several levels (the national healthcare system, clinicians, patients etc.) and by several factors. Importantly, in the Danish healthcare system, treatment of T2DM with GLD (including patients with concomitant CVD) is mainly managed by general physicians.³⁷ In light of the fast-evolving field of diabetes research, a certain time lag is to be expected between the first presentation of positive cardiovascular outcome results to actual implementation in clinical practice³⁸ (Table S3). A great responsibility lies on both general physicians and diabetes specialists supporting primary care to collaborate and minimize delays in implementing new knowledge. In addition, per tradition, specialists involved in the treatment of patients with CVD (eg, cardiologists, neurologists etc.) have not been involved in GLD treatment.^{22,23} Furthermore, the high costs of most cardioprotective GLDs may negatively impact their use even if patient expenses are partly reimbursed by public or private health insurance.^{38,39} Other potential barriers to cardioprotective GLD initiation may include challenges with polypharmacy (including the use of other GLDs),⁴⁰ exclusive focus on reaching glycaemic targets with a given therapy rather than focus on a possible combination of GLDs that include a cardioprotective SGLT2 inhibitor or GLP-1 analogue,⁴¹ and/or fear of hypoglycaemia.

We expected a lag in time to initiation of cardioprotective GLDs in patients with T2DM as their latest diagnosis, compared to CVD as the latest diagnosis, as the former patients, by definition, initiated a GLD (although most often metformin) on the index date. Indeed, patients with CVD as the latest diagnosis seemed to have a faster initiation of cardioprotective GLDs, although the difference was not very large in absolute terms and is of questionable clinical relevance. We expected a larger difference in cardioprotective GLD initiation between the two subgroups but the difference may have been attenuated by barriers specific to either group. For instance, patients with established T2DM and new CVD may already have attempted cardioprotective GLD use at an earlier point in time and discontinued therapy prior to the first CVD event. Furthermore, the recovery after a first CVD event may be complicated (intensive care, physical/psychological rehabilitation, initiation of other important medications) and may prolong the time to initiation of drugs that protect against recurrent CVD events, a situation that is less likely in patients with established CVD and new T2DM.

We found the incidence of SGLT2 inhibitor initiation to increase faster than for GLP-1 analogues between 2012 and 2018. This was not surprising given their later introduction to the market than GLP analogues. Also, SGLT2 inhibitors were the first of the two drugs to show cardiovascular benefit (EMPAREG 2015¹¹ vs. LEADER 2016⁸). From a user perspective, SGLT2 inhibitors may be easier to implement as they are administered orally in contrast to GLP-1 injections and the cost range of SGLT2 inhibitors is lower than GLP-1 analogues.

The present study is based on observational data from national registries with the inherent limitations of a retrospective design. Of special note, the diagnosis of T2DM was defined by the use of GLDs,

thus patients with T2DM who were treated with diet and lifestyle therapy alone were not included in the study population, and study results may therefore not apply to these patients. On the other hand, our definition of T2DM has previously been shown to identify T2DM with high accuracy²¹ and recently we have also found high positive predictive values for the CVD diagnosis and procedural codes used in this study.^{28,29} Therefore, the study population represents a group of patients in whom the vast majority will meet current guideline recommendations for cardioprotective GLD initiation. A further strength of this study, increasing the external validity of our results, is that the study population is drawn from a source population consisting of all individuals living in Denmark and, as such, our study population represents a very broad spectrum of patients. On the other hand, it should be noted that the access to cardioprotective GLDs (costs, re-imbusement programmes, the focus on the use of cardioprotective GLDs among clinicians involved in diabetology etc.) may be very different in countries other than Denmark. Another limitation is that laboratory data (eg, HbA1c) were only available in a subgroup of patients and, consequently, analyses including these data were limited.

In conclusion, the time to initiation of SGLT2 inhibitors and GLP-1 analogues in patients with a dual diagnosis of T2DM and CVD has decreased between 2012 and 2018. However, the proportion of patients with T2DM and CVD initiating cardioprotective GLDs remains low within 2 years after the dual diagnosis, regardless of which part of the dual diagnosis that came last. Barriers to initiating new cardioprotective GLDs and how to overcome them should be a high priority for all parties involved in the care of patients with T2DM and CVD.

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K.L.F., J.S.K., R.W.T., T.K.H. and E.L.G. designed the study. J.S.K. obtained the data. K.L.F. drafted the manuscript, which was critically revised by all authors. The final version of the manuscript was approved by all authors.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

KLF, JSK, RWT and ELG designed the study. JSK obtained the data and made the statistical analysis. KLF drafted the first manuscript, which was critically revised by all authors. The final version of the manuscript was approved by all authors.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14245>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from The Danish Health Data Authority. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of The Danish Health Data Authority.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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